Synthesis of Conjugated Octadecadiynoic Acids

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ABSTRACT

Conjugated 6,8-, 7,9-, 8,10-, and 9,11-octadecadiynoic acids were prepared. In the oxidative coupling of 6-heptynoic acid and 1-undecyne to yield the above 6,8-acid, an excess of undecyne is required. Equal molecular amounts yield chiefly the symmetrical tetradecadiyndioic acid. A method is described for the preparation of a clear cuprous chloride solution having increased catalytic activity.

INTRODUCTION

The importance of acetylenic or ynoic acids as intermediates in the synthesis of unsaturated fatty acids of known structure is well established. In this paper the syntheses of four octadecadiynoic acids having conjugated acetylenic bonds at the 6,8, 7,9, 8,10, and 9,11 positions, respectively, are described. These were accomplished by coupling the appropriate acetylenic acids with 1-alkynes.

Black and Weedon (1) oxidatively coupled 10-undecynoic acid and 1-octyne to form 10,12-nonadecadiynoic acid. The 10-undecynoic acid was prepared from commercially available 10-undecenoic acid. They also demonstrated how the ethyl ester of 10-undecynoic acid could be degraded by means of phenyl magnesium bromide to form a tertiary alcohol, dehydratable to a hydrocarbon. The hydrocarbon was then oxidized to yield the 9-decynoic acid for coupling purposes.

The production of a series of shorter chain ynoic acids by degradation of 10-undecynoic acid as starting material becomes impractical. This paper describes a different approach for the synthesis of a series of ynoic acids, namely, 6-heptynoic, 7-octynoic, 8-nonynoic and 9-decynoic acids. Isenberg et al. (2) described a method for preparing ω-bromo normal fatty acids by the oxidation of cycloketones to lactones, followed by the treatment of the lactones with hydrobromic acid. We utilized his results and condensed ω-bromo acids with sodium acetylide to yield acetylenic acids. The results are described below.

In the coupling of an acetylenic acid and an alkyne, one unsymmetrical and two symmetrical reactions are possible. The unsymmetrical is the desired reaction. When Black and Weedon oxidatively coupled the relatively long-chained 10-undecynoic acid and 1-hexyne, the yield of 10,12-heptadecadiynoic acid was 30%. In this investigation, it was necessary to modify the procedure when the relatively short 6-heptynoic acid and 1-undecyne were coupled; otherwise, the 6-heptynoic acid coupled symmetrically nearly exclusively to form tetradecadiyndioic acid.

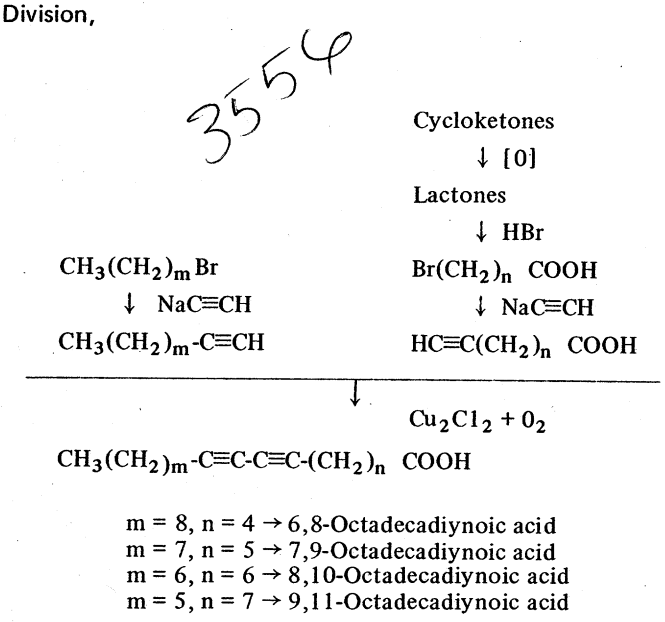
The following outline shows the fundamental reactions in the preparation of the diynoic acids.

TABLE I

Comparison of Yields of Alkynes

1-Alkynes	Without DMF,[a] %	With DMF, %
Heptyne	65	----
Octyne	63	61
Nonyne	56	----
Decyne	45	83
Undecyne	58	68

[a]Dimethylformamide.



m = 8, n = 4 → 6,8-Octadecadiynoic acid
m = 7, n = 5 → 7,9-Octadecadiynoic acid
m = 6, n = 6 → 8,10-Octadecadiynoic acid
m = 5, n = 7 → 9,11-Octadecadiynoic acid

EXPERIMENTAL PROCEDURES

Materials

Alkynes were prepared from 1-bromohexane, 1-bromoheptane, 1-bromooctane and 1-bromononane. Monoacetylenic acids were synthesized from cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone. The condenser for liquid ammonia consisted of a coil of six turns of 0.5 in. i.d. aluminum tubing, supported in an insulated galvanized iron container, filled with dry ice and alcohol. All reactions were performed in a laboratory hood, and those involved with peroxy acids were shielded for safety.

Procedures

Synthesis of 1-Alkynes. The four alkynes were first prepared by the method of Greenlee (3) as described by Jacobs (4). Sodium acetylide was prepared in liquid ammonia and then a 1-bromoalkane was added fairly rapidly from a dropping funnel to the liquid ammonia solution.

The second procedure used in synthesizing two of the larger alkynes combined two different published methods. Campbell and Campbell (7) described a convenient way for preparing sodium acetylide and also prepared some of the 1-alkynes of low molecular weight but stated that the method was not satisfactory for the preparation of alkynes above octyne. Jenny and Meier (8) prepared sodium acetylide in liquid ammonia, and then replaced the ammonia with dimethylformamide. These procedures are demonstrated with the synthesis of 1-decyne as an example.

Sodium acetylide was prepared by adding 12.5 g sodium (0.543 g atom) and acetylene gas to 300 ml liquid ammonia in a 3:1 three-necked flask connected to a dry ice condenser (7). At the conclusion of this reaction, the acetylene was shut off. 1-Bromooctane (105 g, 0.543 mole), diluted with 200 ml of dry dimethylformamide, was added rapidly, dropwise, to the liquid ammonia solution (8). The reflux condenser was removed and the ammonia allowed to evaporate at room temperatture. The paste remaining in the flask was thoroughly stirred and more dimethylformamide added, if necessary, to form a liquid suspension. The mixture was heated 3 hr at 60-70 C and mechanically stirred. The product was extracted with ether,

and the final residue distilled to obtain the 1-decyne.

Table I shows the yields of some of the 1-alkynes produced by the two methods, with and without dimethylformamide (DMF). The final reaction temperature with DMF is 60-70 C; otherwise, the temperature is that of liquid ammonia.

Synthesis of ω-Bromoalkanoic Acids. Four bromoacids (ω-bromopentanoic, ω-bromohexanoic, ω-bromoheptanoic and ω-bromooctanoic acids) were prepared by oxidation of the appropriate cycloketone with peroxytrifluoroacetic acid (2,5), followed by bromination of the isolated crude lactone and hydroxy acid by treatment with 48% hydrobromic acid.

Another method of oxidation of the cycloketones using 25% peracetic acid, followed the procedure of Phillips and Starcher (6) except that acetic acid instead of acetone was used as solvent.

In all the oxidations approximately 0.3 mole of the cycloketone was used as starting material. The bromoacids, melting points and yields by the two methods are given in Table II.

Synthesis of Alkynoic Acids. The procedure (4) for the preparation of alkynoic acids and for alkynes was quite similar except that the ω-bromoacid required twice the molecular equivalent of sodium acetylide because of the carboxyl acidic hydrogen. Since the bromoacids are solids, they were added to the reaction mixture from a dropping funnel as ether solutions. The following alkynoic acids were prepared: heptynoic, yield 70%; octynoic, 52%; nonynoic, 34%; and decynoic, 42%. Only octynoic acid, yield 72%, was also prepared (7,8) by the use of DMF. There are indications that the yields would be higher by this method.

Oxidative Coupling of an Alkyne and an Alkynoic Acid. A modification of the method of Black and Weedon (1) was used. For the shorter-chain alkynoic acids, it was found desirable to increase the relative molecular amounts of the alkyne to alkynoic acid, 3 to 1, in order to decrease the self-coupling of alkynoic acid to form diyndioic acid. Conversely, the larger alkynes had less tendency for symmetrical coupling. Purification of the cuprous chloride solutions was also advantageous, since commercial cuprous chloride is subject to air oxidation.

Example: Preparation of 6,8-Octadecadiynoic Acid. Sulfur dioxide was bubbled through a yellowish suspension of 12 g cuprous chloride and 36 g ammonium chloride in 250 ml of water until the solution became clear (10 to 15 sec) and all the cuprous chloride dissolved except for some of the larger lumps. The solution was then boiled until all odor of sulfur dioxide in the vapor had disappeared. The container was covered with a watch glass during boiling of the solution. (Access of air causes some darkening.) The solution was cooled and the volume of the slightly yellow solution was adjusted to approximately 200 ml. The calculated amount of concentrated hydrochloric acid was added to make the solution approximately 0.1 N. This cuprous chloride solution was then poured into an Erlenmeyer flask containing 5 g of ethyl 6-heptynoate and 15 g 1-undecyne dissolved in 100 ml of 95% ethyl alcohol. The reaction flask was connected to an oxygen source and a manometer and shaken at room temperature until absorption ceased. The reaction mixture was transferred to a separatory funnel and diluted with 400 ml of 2 N hydrochloric acid. The solution was extracted with ether, the ether washed with water until free of acid and evaporated. The residue was transferred to an Erlenmeyer flask by means of 100 ml alcohol and the oxidation procedure repeated as above. Similarly, at the end of the second oxidation, the ether extract was again obtained.

TABLE II

Synthesis of ω-Bromoalkanoic Acids

Bromoacid	Melting, C	Methods, Yields %[a] Peroxy-trifluoro-acetic acid	Peroxy-acetic acid
5-Bromopentanoic	40.0-40.5	45	74
6-Bromohexanoic	33.8-34.4	40	69
7-Bromoheptanoic	30.3-30.8	45	16
8-Bromooctanoic	36.4-36.8	27	----

[a]Based on cycloketone

The ether residue, consisting of ethyl esters and hydrocarbons, was saponified with 0.5 N alcoholic sodium hydroxide solution for 1/2 hr. The solution was diluted with water and extracted with ether to remove the hydrocarbons. The solution was then acidified and again extracted with ether to obtain the free acids. After washing the ether solution free of mineral acid, the ether residue was crystallized from petroleum ether-acetone mixture at 0 C. The crystallized product was chiefly 6,8-tetradecadiyndioic acid. The mother liquor was placed at -22 C for crystallization of 6,8-octadecadiynoic acid.

The excess 1-undecyne used in the reaction was recovered from the hydrocarbon residue by distillation, the docosadiyne remaining in the pot.

Purification of Acids. Sparreboom (9) separated 10-undecynoic acid from 10,12-octadecadiynoic acid by treating water solutions of their ammonium salts with magnesium sulfate. The magnesium salt of 10,12-octadecadiynoic acid precipitated; the 10-undecynoic soap remained in solution. This procedure can also be applied to the separation of octadecadiynoic acids from the diyndioic acids, which in spite of their great differences in solubility in organic solvents, tend to cocrystallize considerably.

A mixture of 9,11-octadecadiynoic and symmetrical eicosadiyndioic acids (3 g) was dissolved in 200 ml of aqueous ammonium hydroxide. The magnesium salt of octadecadiynoic acid was precipitated by the addition of 30 ml of 10% ammonium chloride solution and excess of 15% magnesium sulfate solution. The eicosadiyndioic acid soap remained in solution. The insoluble soap was filtered off, washed, acidified and dissolved in ether. The octadecadiynoic acid was crystallized from light petroleum at -20 C. The soluble soap solution was likewise acidified and the free acids recovered by ether extraction, washed and crystallized from light petroleum-acetone mixture at O C.

Table III lists the compounds prepared and purified by

TABLE III

Compounds Formed by Oxidative Coupling

Diynoic acids	Melting, C	Yield, %	Diyndioic acids	Melting, C	Yield, %
6,8-Octadecadiynoic	56.5-57	26	6,8-Tetradecadiyndioic	175	54
7,9-Octadecadiynoic	51.5-52	29	7,9-Hexadecadiyndioic	129.5-130	48
8,10-Octadecadiynoic	41.5-42	28	8,10-Octadecadiyndioic	135-135.5	26
9,11-Octadecadiynoic	46.5-47	42	9,11-Eicosadiyndioic	122-122.5	20

the above method. The 8,10- and 9,11-octadecadiynoic acids were each prepared by a single oxidative treatment. These conjugated diynoic acids are very stable to oxidation in spite of the fact that they readily turn blue when exposed to light. The formation of the blue compound appears to be a surface phenomenon, the blue compound being a thin film which protects the underlying compound from further action to light. Such compounds can be purified by dissolving them in acetone or light petroleum. As an example, 3.70 g of 6,8-octadecadiynoic acid, deep blue in color, had stood for 1 1/2 years in a loose-fitting enclosure with no attempt to exclude atmospheric oxygen. When the sample was dissolved in acetone, the blue compound immediately changed to red and remained in suspension as a finely divided insoluble compound. On filtering, the filtrate was a clear colorless solution of pure 6,8-octadecadiynoic acid and the red residue on the filter paper formed a tissue-like film that could be peeled from the filter paper. Weight of film was .0083 g or 0.2% of sample.

DISCUSSION

The peracetic acid method was much superior to that of the peroxytrifluoroacetic acid for the oxidation of cyclopentanone and cyclohexanone as shown (Table II) in the resulting yields of bromopentanoic and bromohexanoic acids. However, the peroxytrifluoroacetic acid method was much better for the oxidation of cycloheptanone and cyclooctanone, although the yields were nevertheless low.

It appeared that the larger molecules were more difficult to oxidize. The greater success with the use of peroxytrifluoroacetic acid (5) was probably due to the difference in procedure. At the beginning of the reaction, there was a high concentration of peroxytrifluoroacetic acid in the reaction flask, and the cycloketone to be oxidized was added dropwise to the reaction mixture. Conversely, in the peroxyacetic acid method (6), the cycloketone was in the reaction flask and the peroxyacetic was added dropwise. The latter procedure was safer but had a lower oxidation potential at the beginning of the reaction.

Most of the oxidation of the cycloketone appeared to take place with the first fraction of cycloketone added, as indicated by the increase in temperature of the peroxytrifluoroacetic acid mixture. After half the cycloketone had been added, the cycloketone could be added much more rapidly with little temperature change resulting. In one run during the early addition of cycloheptanone to the peroxytrifluoroacetic acid, the rate of flow from the dropping funnel changed due to vibration from the stirrer, and the temperature rapidly went to 50 C before the addition was stopped. This indicated that the peroxide mixture was fairly stable at the higher temperature, although the aim was to maintain the temperature at 10-15 C.

In the oxidation of cyclooctanone, the solid was dissolved in acetone so that it could be added dropwise, the usual procedure, but the last quarter of the cyclooctanone was added to the reaction mixture, in small amounts, as a solid which dissolved rapidly and caused little temperature change. The synthesis was normal, except that the yield was lower than usual. In one experiment, to avoid the use of acetone as a solvent, a small amount of solid cyclooctanone was added directly to the reaction mixture. About half a second after the solid touched the solution of peroxytrifluoroacetic acid, a violent explosion took place. In spite of the efficient stirring of the mixture, the solid probably permitted a local increase in temperature to the point of detonation. This result is reported for the safety of workers in this field.

The original purpose of this investigation was the preparation of *cis,cis*-octadecadienoic acids through the selective hydrogenation of diynoic acids with Lindlar's catalyst (10). After preparing many different Lindlar catalysts and using them in hydrogenations, the writer believes the successful preparation of such a partially-poisoned catalyst, especially for conjugated diynoic acids, is highly fortuitous, depending on the materials used and the structure of the compound being hydrogenated. When there is one triple bond, or the triple bonds are well separated in the molecule, the problem is much simpler. Stroink and Sparreboom (11), using Lindlar's catalyst, were very successful in the selective hydrogenation of 7,15-, 8,15-, and 9,15-octadecadiynoic acids.

The difficulties encountered with the Lindlar catalyst in these hydrogenations led to experiments with other methods of hydrogenation such as the use of diimide reductions (12) and powdered zinc in neutral solutions (13). The powdered zinc method appeared to be the more promising and these investigations will be reported later.

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